

Charge-Transfer Complex Promoted C-N Bond Activation for Ni-**Catalyzed Carbonylation**

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S Supporting Information

ABSTRACT: A new strategy was developed for activation of C-N bond via formation of an amine- I_2 charge-transfer complex, which facilitates the inert C-N bond activation via oxidative addition with Ni(0). This strategy has been successfully applied in the Ni-catalyzed carbonylation of



benzylamines via direct insertion of CO into the C-N bond, which provided a straightforward and rapid approach to arylacetamides in the presence of catalytic amounts of I_2 and Ni catalyst. Mechanistic studies suggested that a benzyl radical generated via the oxidative addition was involved in the present reaction.

he C–N bond is one of the most ample chemical bonds and exists in myriad organic molecules and naturally occurring biomacromolecules.¹ The ability to directly insert small molecules or unsaturated chemical bonds into the C-N bond is highly desirable for the late-stage derivatization of complex molecules.² In this context, the direct insertion of CO into the C-N bond of amines via C-N bond activation has been proven to be one of the most direct and promising pathways to access a range of valuable amides.³ However, the full potential of this strategy has not yet been realized, and most of those reactions are only feasible for energetically favored three- or four-memberedring nitric heterocycles, active allylamines, or propargylamines,⁴ in large part due to the formidable challenge of activation of simple C-N bonds.

As for the activation of the C-N bond of tertiary amines, the most promising method with transition metals would be oxidative addition of an amine to a low-valent metal center.⁵ However, the direct activation of simple C-N bonds via oxidative addition is still a great challenge exacerbated by their high bond dissociation energy and high δ -donation ability of the nitrogen atom.⁶ One promising strategy to facilitate the oxidative addition is improving the redox potential of the amines to enhance the π -back bonding by decreasing the electron-density of the nitrogen atom. In this context, several catalytic approaches have been developed to cleave the C-N of benzylamines by conversion of the simple amines to quaternary ammonium salts (Scheme 1, top). However, only the resultant carbon moiety was used as a coupling partner for the subsequent C-C bond formation process in these reactions; thus, the cleaved amine moiety was discarded, leading to wasteful byproduct generation and low atom-efficiency.⁷ Therefore, the development of efficient C–N bond activation strategies that are capable of utilization of

Scheme 1. Transition-Metal-Catalyzed C-N Bond Activation





both of the carbon and nitrogen nucleophiles generated by the C–N bond cleavage with high atom economy is highly desirable.

The charge-transfer complex (CT complex) is an association of two or more molecules, or of different parts of one large molecule, in which a fraction of electronic charge is transferred between the molecular entities.⁸ Because of electron-transfer, the original chemical bonds experience polarization, thus improving the redox potential and weakening the chemical bonds. Iodine is one kind of good electron acceptor for its shortage of one electron to a full octet, which has been widely used for the formation of CT complexes with amines.⁹ It would be reasonable to believe that iodine is capable of promoting the oxidative addition of amine with low-valent metal via formation of an

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amine–iodine CT complex. Once the C–N bond is cleaved by a transition metal, the CO would be inserted into the C–N bond to furnish a catalytic carbonylation reaction under appropriate conditions (Scheme 1, bottom). Herein, we report the successful realization of this concept in a Ni-catalyzed carbonylation that allows the introduction of CO into the C–N bond of benzylamines via charge-transfer complex promoted C–N bond activation. The reaction can be carried out in the presence of a catalytic amount of iodine and NiCl₂, which constitutes a straightforward and 100% atom-efficient approach to amides.

To identify whether the CT complex could be formed between the I_2 and the tertiary amine 1, the corresponding control experiments were conducted and monitored by NMR spectra. The ¹H NMR spectra of a solution of tribenzylamine in CDCl₃ showed a cleanly resolved single peak at 3.55 ppm for the CH_2N protons, with no significant alteration between 25 and 50 °C. However, when 1 equiv of I2 was added to this solution, a new signal appeared at 4.07 ppm for the CH_2N protons, and the signal at 3.55 ppm for the free CH_2N protons nearly disappeared with time going on. Furthermore, the same signal at 4.07 ppm was also observed when a catalytic amount of I₂ was introduced into the solution of tribenzylamine in CDCl₂. Control experiments ruled out that the benzyl iodide was formed in this reaction mixture (see the Supporting Information). These results can be interpreted by considering the fact that the CT complex of amine-I2 was indeed formed.⁹¹ In contrast, no new signal was observed when the I₂ was introduced into the solution of N₁Ndibenzyl-2-phenylacetamide in CDCl₃, which suggested that the amide-I₂ complex was not formed due to the lower electrondonating ability of the amide-nitrogen atom.

The above positive results intrigued us to investigate the carbonylation reaction of benzylamines with CO via the CT complex enabled C-N bond activation according to the proposed reaction pathway (Scheme 1). N,N-Diisopropylbenzylamine (1a) was chosen as a model substrate to identify a suitable metal complex and reaction conditions. Various metal complexes, including palladium and nickel, were tested as catalysts. After extensive experimentation, $Ni(cod)_2$ proved to be a promising catalyst for promoting the desired reaction. The desired amide 2a was obtained in 34% yield when BINAP was utilized as a ligand under 20 atm of CO at 140 °C in the presence of a catalytic amount of I₂.¹⁰ Further evaluation of the phosphine ligand (Table 1, entries 1-5) demonstrated that the 2-(diphenylphosphino)benzoic acid (L1) stood out as the best ligand to deliver the desired amide in 72% yield (Table 1, entry 5). Furthermore, the impact of the nickel catalyst precursors was carried out with L1 as a ligand, revealing that the inexpensive and commercially available NiCl₂ was the most effective catalytic precursor for this reaction to give the desired product 2a in 73% isolated yield (Table 1, entry 6). Other simple nickel salts or complexes such as NiBr₂, NiI₂, Ni(acac)₂, and Ni(PPh₃)₄ were also effective for this transformation to give the desired product **2a** in moderate to good yields (Table 1, entries 7-10). Screening of some representative solvents revealed that the most efficient catalysis was furnished in anisole (Table 1, entry 6). To our delight, the reaction could be completed under 10 atm of CO to yield the corresponding product in 73% isolated yield (Table 1, entry 16). When the catalyst loading of I₂ was further decreased to 15 mol %, the desired product 2a was still obtained in 77% isolated yield under 10 atm of CO. Control experiments demonstrated that no reaction occurred when the reaction was conducted in the absence of either I_2 or Ni catalyst (see the SI), indicating the critical importance of the I₂ and Ni catalyst for

Table 1. Screening of Reaction Conditions^a

	∕∕ <mark>N</mark> (<i>i</i> -Pr) ₂ + <mark>CO</mark> − 1a	[Ni]/L (5 mol %) I ₂ (20 mol %) solvent, 140 °C		N(i-Pr) ₂
entry	[Ni]	ligand	solvent	yield (%)
1	Ni(cod) ₂	BINAP	anisole	34
2	$Ni(cod)_2$	Xantphos	anisole	33
3	$Ni(cod)_2$	DPPF	anisole	7
4	$Ni(cod)_2$	DPEphos	anisole	22
5	$Ni(cod)_2$	L1	anisole	72
6	NiCl ₂	L1	anisole	78 (73)
7	NiBr ₂	L1	anisole	71
8	NiI ₂	L1	anisole	65
9	$Ni(acac)_2$	L1	anisole	68
10	Ni(PPh ₃) ₄	L1	anisole	75
11	NiCl ₂	L1	PhCF ₃	70
12	NiCl ₂	L1	toluene	34
13	NiCl ₂	L1	dioxane	54
14	NiCl ₂	L1	DMF	<5
15	NiCl ₂	L1	NMP	<5
16 ^b	NiCl ₂	L1	anisole	77 (73)
$17^{b,c}$	NiCl ₂	L1	anisole	$82(77)^{d}$
18	NiCl ₂		anisole	51

^{*a*}Reaction conditions: **1a** (0.5 mmol), [Ni] (0.025 mmol), I₂ (0.1 mmol), ligand (0.03 mmol), **L1** = 2-(diphenylphosphino)benzoic acid (0.06 mmol), solvent (2 mL), CO (20 atm), 140 °C, 18 h. Yields were determined by GC using *n*-tetradecane as an internal standard, and isolated yields are given within parentheses. ^{*b*}CO (10 atm). ^{CI}₂ (0.075 mmol). ^{*d*}4% phenyl 2-phenylacetate was isolated as a byproduct.

activation of the C–N bond. However, the target product 2a was obtained in 52% yield in the absence of ligand (Table 1, entry 18), which revealed that the ligand is not essential for the present catalytic system.

Having established the optimized reaction conditions, the substrates with different substituents on the nitrogen atom were investigated under the standard conditions. As summarized in Table 2, tertiary benzylamines containing different groups on the nitrogen atom (1a-h) gave the desired product in distinctly

Table 2. Substrate Scope of Benzylamines^a

	NR ₂	+ CO -	NiCl ₂ /L1 (5 mol %) l ₂ (15 mol %) anisole, 140 °C 2			
			yield ^b (%)			
entry	substrate	R	conditions A	conditions B	conditions C	
1	1a	<i>i</i> -Pr	77	73		
2	1b	Н	<5	<5		
3	1c	CH_3	<5	<5	38	
4	1d	Et	<5	14	67	
5	1e	<i>n</i> -Pr	19	35	73	
6	1f	Bn	59	73		
7	1g	Су	68	65		
8	1h	Ph	8	14	73	

^aConditions A: **1** (0.5 mmol), CO (10 atm), NiCl₂ (0.025 mmol), I₂ (0.075 mmol), **L1** (0.06 mmol), anisole (2 mL), 140 °C, 18 h. Conditions B: **1** (0.5 mmol), CO (20 atm), NiCl₂ (0.025 mmol), I₂ (0.1 mmol), **L1** (0.06 mmol), anisole (2 mL), 140 °C, 18 h. Conditions C: **1** (0.5 mmol), CO (20 atm), NiCl₂ (0.05 mmol), I₂ (0.1 mmol), **L1** (0.12 mmol), anisole (2 mL), 140 °C, 48 h. ^bIsolated yield.

different yields. For the benzylamines with isopropyl (*i*-Pr), benzyl (Bn), and cyclohexyl (Cy) as substituents, the carbonylation adduct **2** could be obtained in good yields even under relatively mild conditions (Table 2, entries 1, 6, and 7). When other nitrogen groups, such as NH₂, N(CH₃)₂, NEt₂, N(*n*-Pr)₂, and NPh₂, were installed in the benzyl skeleton, the conversion was dramatically decreased under conditions A or B. To our delight, the desired adducts **2d**, **2e**, and **2h** could be obtained in good yields by increasing the catalyst loading and prolonging the reaction time (Table 2, entries 4, 5, and 8). The relatively lower activity of these substrates might be attributed to either the difficult cleavage of the corresponding C–NR₂ bonds or the reluctance for undergoing the reductive elimination.

On the basis of the results described above, a variety of benzylamines with two isopropyl groups attached on the N atom were subjected to the nickel-catalyzed C-N bond carbonylation reactions to investigate its substrate scope and generality (Table 3). A series of substituents regardless of electron-donating or -withdrawing properties on the phenyl ring of the tertiary benzylamines were well tolerated, providing the desired adducts in moderate to good yields (50-77% yields). Typical functional groups, such as halides, ether, ester, ketone, cyano, and sulfonylamide, were compatible with this method (Table 3, entries 2-16), giving ample opportunities for further elaboration by transition-metal-catalyzed coupling or other reactions. In addition to phenyl-substituted amines, naphthyl-substituted amines were also compatible with this reaction, generating the corresponding amides (2x and 2y) in good yields (Table 3, entries 17 and 18). To our great delight, reaction of a heteroarylsubstituted amine such as N-isopropyl-N-(thiophene-2ylmethyl)propan-2-amine also proceeded smoothly to provide the carbonylation product in moderate yield under modified reaction conditions (Table 3, entry 19). However, only a lower yield was obtained for the α -substituted benzylamine (Table 3, entry 20). Unfortunately, no desired reaction occurred for the α disubstituted benzylamines. Furthermore, allylamines and propargylamines were found to be incompatible with these reaction conditions (see the SI). The structures of 2w and 2z were confirmed by single-crystal X-ray diffraction.¹¹

To gain further insight into the mechanism, the following control experiments were carried out (Scheme 2). When radical scavenger TEMPO was introduced into the standard reaction, the desired product could not be obtained. In addition, when 1,1-diphenylethylene was introduced into this carbonylation system, the benzylic adduct 3 was obtained in 40% yield and almost no desired carbonylation product was detected, which suggested that a free-radical process was most likely involved in this carbonylation reaction. Competition reaction between 1f and 1k produced four kinds of amides, which indicated that an outersphere electron-transfer pathway was involved in the present reaction for transferring the benzyl radical to the desired product (see the SI).

While a precise reaction mechanism is not yet clear at the present stage, the most plausible mechanism in line with our experimental results and previous reports on Ni-catalyzed carbonylation reactions¹⁰ is illustrated in Figure 1. Initially, the amine–I₂ charge-transfer complex **A** was most likely formed, which underwent oxidative addition with an active Ni(0) center to form the radical-containing Ni(I) complex **B** via a radical pathway. Then acylnickel(I) species **C** was generated by CO migratory insertion along with the release of I₂ due to the lower electron density of the amide moiety. Subsequently, oxidative addition of the benzylic radical to the active Ni(I) center of

 Table 3. Substrate Scope of Benzylamines^a



^aConditions A: **1** (0.5 mmol), CO (10 atm), NiCl₂ (0.025 mmol), I₂ (0.075 mmol), **L1** (0.06 mmol), anisole (2 mL), 140 °C, 18 h. Conditions B: **1** (0.5 mmol), CO (20 atm), NiCl₂ (0.025 mmol), I₂ (0.1 mmol), **L1** (0.06 mmol), anisole (2 mL), 140 °C, 18 h. Conditions D: **1** (0.5 mmol), CO (30 atm), NiCl₂ (0.05 mmol), I₂ (0.1 mmol), **L1** (0.12 mmol), anisole (2 mL), 150 °C, 18 h. ^bIsolated yield. ^cPhCF₃ as solvent.

intermediate **C** via outer-sphere electron-transfer delivered the acylnickel(II) species **D**, which underwent reductive elimination to deliver the desired amide **2** and regenerated the active Ni(0) to complete the catalytic cycle.¹²

In summary, we have developed a new strategy for activation of inert C–N bonds by using a catalytic amount of I_2 for formation of the amine– I_2 charge-transfer complex. This strategy has been

Scheme 2. Control Experiments



Figure 1. Plausible reaction mechanism.

successfully applied in the first nickel-catalyzed direct carbonylation of benzylamines via C–N bond activation. This new transformation is characterized by a broad substrate scope and represents a concise, operationally simple, and useful method for the preparation of amides that are of interest in synthetic organic chemistry. It is anticipated that this line of research could open a new pathway for C–N bond transformation and could widen the category of inert bond activation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01488.

Detailed experimental procedures, compound characterization data, and NMR spectra (PDF) Crystallographic data for compound **2w** (CIF)

Crystallographic data for compound 2z (CIF)

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(11) CCDC 1524398 (2w) and 1524399 (2z) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) The mercury-poisoning experiments suggested that the Ninanoparticle is produced in the present reaction, which further proved that Ni(0) might be involved in the catalytic cycle.